PB82-118217

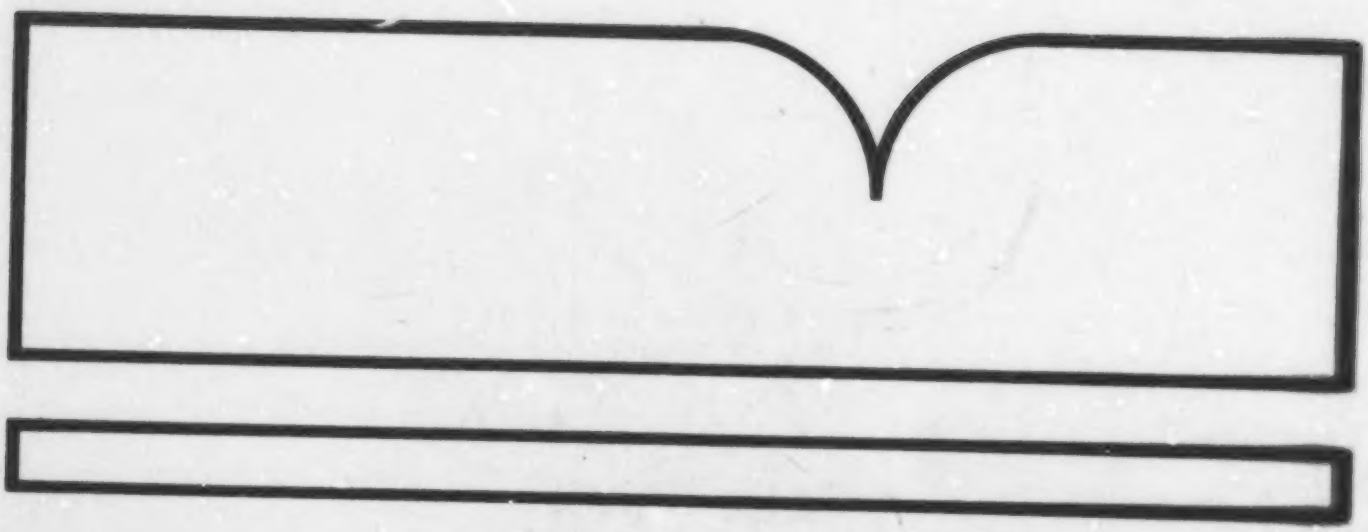
Air Pollution and Respiratory Disease

Stanford Univ., CA

Prepared for

Health Effects Research Lab.
Research Triangle Park, NC

Sep 81



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TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO.	2.	3. RECIP
EPA-600/J-81-335	JOURNAL ARTICLE	PB82-118217

4. TITLE AND SUBTITLE	5. REPORT DATE
AIR POLLUTION AND RESPIRATORY DISEASE	September 1981
	6. PERFORMING ORGANIZATION CODE 307087

7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
ALICE S. WHITTEMORE	

9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
Department of Family, Community, and Preventive Medicine Stanford University School of Medicine Stanford, California 94305	AAGA1D
	11. CONTRACT/GRANT NO. Grant No. R-804932

12. SPONSORING AGENCY NAME AND ADDRESS	13. TYPE OF REPORT AND PERIOD COVERED
Office of Research and Development (RTP, NC) Health Effects Research Laboratory US Environmental Protection Agency Research Triangle Park, North Carolina 27711	14. SPONSORING AGENCY CODE EPA-600/11

15. SUPPLEMENTARY NOTES

Published In: Annual Review of Public Health 2: 397-429, 1981

16. ABSTRACT

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17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA 22161

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS (This Report)	21. NO. OF PAGES
RELEASE TO PUBLIC	UNCLASSIFIED	
	20. SECURITY CLASS (This page) UNCLASSIFIED	22. PRICE

EPA-600/J-81-335
Journal Article

Ann. Rev. Public Health. 1981. 2:397–429

AIR POLLUTION AND RESPIRATORY DISEASE

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If you visit American city,
You will find it very pretty.
Just two things of which you must beware:
Don't drink the water and don't breathe the air.

Pollution, pollution,
Wear a gas mask and a veil.
Then you can breathe, long as you don't inhale.[1]

INTRODUCTION

Concern about polluted air in our urban and industrial areas began gathering momentum shortly after World War II. At that time it seemed obvious that clean air, like clean water, clean food, and a clean body, was a worthwhile goal in itself, requiring no further justification. But it soon became evident that this goal is expensive to attain, and that rigid adherence to stringent standards of cleanliness diverts limited human resources away from other pressing and critical problems. Awareness of such facts has reoriented the goal to one of protecting public health. This emphasis is clearly stated in the US Clean Air Act of 1963: "The Congress . . . finds that the growth in the amount and complexity of air pollution brought about by urbanization, industrial development, and the increasing use of motor vehicles, has resulted in mounting dangers to the public health and welfare" (1). Two decades later we ask: What do we know of these dangers and what must we do to improve our knowledge?

[1]From "That Was the Year that Was." Music and lyrics by Tom Lehrer, copyright © 1965 by Tom Lehrer. Reprinted by permission.

0163-7525/81/0510-0397$01.00

We know from "killer fogs" in the period from 1930 to 1960 that very high levels of air pollution for several days can be fatal. These episodes, during which hospital admissions and deaths increased dramatically, provide the clearest evidence of human hazard due to smoggy, dirty air. They have motivated clean air legislation in many of the industrialized nations of the world.

The Clean Air Acts of Great Britain in 1956 and of the US from 1963 to 1970 differ considerably in their underlying control strategies. The former has reduced ambient levels of soot and smog simply by restricting the grossly inefficient burning of coal in domestic open fires. The US Clean Air Amendments of 1970, on the other hand, mandate the promulgation of national air quality standards for each of several distinct pollutant species. Those currently regulated and their standards are shown in Table 1. Unlike the British approach, the US standards are based on the assumptions that the culpable constituents of pollution can be identified, and that "safe" levels of these agents can be determined. As we shall see, these assumptions lead to considerable regulatory difficulty.

On both sides of the Atlantic, legislation and its enforcement have led to sizable reductions in ambient levels of virtually all air contaminants. These trends are evident in Figure 1. Ironically, they present a dilemma: while the evidence of adverse effects due to high levels of air pollution is unquestioned, at the current lower levels effects are extremely difficult to discern. The three strategies for detecting effects are animal experiments, controlled human studies, and epidemiological studies of populations exposed to varying types of ambient air.

Table 1 US primary air quality standards

Pollutant	Standard	Averaging time
SO_2	80 $\mu g/m^3$ (0.03 ppm)	Annual arithmetic mean
	365 $\mu gm/m^3$ (0.14 ppm)	Maximal 24-hr aver.
Total suspended particulates	75 $\mu g/m^3$	Annual geometric mean
	260 $\mu g/m^3$	Maximal 24-hr aver.
Photochemical oxidants	0.12 ppm	Maximal 1-hr aver.
NO_2	100 $\mu g/m^3$ (0.05 ppm)	Annual arithmetic mean
CO	10 mg/m^3 (9 ppm)	Maximal 8-hr aver.
	40 mg/m^3 (35 ppm)	Maximal 1-hr aver.

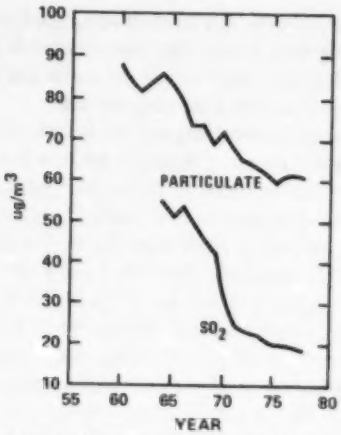

Figure 1 Average annual levels of total suspended particulates and sulfur dioxide in US during 1960 to 1978. Particulate levels represent annual geometric means of daily values averaged over 95 sites during 1960 to 1971 and over 3000 sites during 1972 to 1978. Sulfur dioxide levels represent annual arithmetic means of daily values averaged over 32 sites during 1965 to 1972 and over 1322 sites during 1972 to 1978. Reprinted with permission from William F. Hunt, Environmental Protection Agency, personal communication.

Because the investigator working with animals has relatively close control over experimental conditions, causal relationships are more easily established in animal than in human studies. Further, animal experiments can delineate biochemical and pathophysiological mechanisms for damage due to one or more air pollutants. Such mechanisms can motivate human studies. They can also strengthen a causal basis for associations observed in epidemiological studies. On the other hand, there are problems in extrapolating animal results to man in the face of large interspecies variability in susceptibility to toxic effects. Another limitation of animal studies, shared by controlled human experiments, is their inability to simulate the complex and changing pollutant mix in ambient air.

Controlled laboratory studies of human exposures can provide chemically specific information about which pollutants at which levels produce acute effects. But they cannot identify the effects of long-term exposures to moderate pollutant levels. Moreoever, findings obtained with healthy volunteers may not pertain to sensitive subgroups of the general population. These limitations, together with those noted above for animal studies, force us to turn to epidemiology for detailed information on which to base air quality standards.

Although epidemiological studies can examine the effects of realistic exposures among various population subgroups, they have limited ability to specify which pollutants at which levels produce risk. In addition, they

are insensitive to small effects. All observational studies have at best limited control of intervening factors that can bias relationships of interest. However, those concerning the effects of air pollution are fraught with special difficulties, as discussed in the following sections.

I limit this review to epidemiological studies of the role of ambient air pollution in respiratory disease. I evaluate what is known and what needs to be known in this area in order to determine pollutant levels leading to tolerable health risks. Because animal studies, controlled human studies, and nonrespiratory hazards are not considered, I make no general assessment of the current US standards. Instead, I argue that the epidemiological studies considered do not provide an adequate basis for establishing the dose-response relationships needed to set standards. The two sections below contain a brief description of air pollution, and a critical survey of some recent evidence relating air quality to respiratory mortality and morbidity, especially morbidity. This is followed by a discussion of the obstacles to be overcome and the outlook for the future.

POLLUTANTS

Contaminants present in ambient air can be classified loosely into four categories: (*a*) sulfur oxides and particulates, (*b*) photochemical oxidants and oxides of nitrogen, (*c*) carbon monoxide, and (*d*) metallic and other pollutants, such as lead, cadmium, asbestos, radon, etc, that frequently are emitted by industrial point sources. This article deals only with the respiratory effects of pollutants in the first two categories. The reader is referred to references (2–11) for reviews of health hazards associated with the remaining pollutants.

Sulfur Oxides and Particulates

Sulfur oxides and particulates are grouped together because they commonly occur simultaneously as the result of fossil fuel combustion. Their common occurrence makes it extremely difficult to indite individual components, e.g. sulfur dioxide, sulfuric acid, sulfate aerosols, hydrocarbons, and inorganic ash, as hazards to health. In addition to fossil fuel combustion, other sources for sulfur oxides are smelters and sulfuric acid manufacturers, while particulates are also generated by such industrial sources as grain elevators, cement works, and lumber mills. These pollutants do not form a chemically or physically specific mixture, but one that varies both geographically and temporally in chemical character, oxidation state, and particle size distribution. Part of this variation is due to the rate and source of emissions, as well as to the meteorology and local topography of the area. Thus associations with respiratory damage found at a particular time and place cannot

be generalized readily. When inhaled, the larger particles are apt to lodge in the nasal and pharyngeal passages and are less likely to be deposited in the lower respiratory tract. For this reason it is the finer particles (<2 to 3 μm in diameter) that are believed to pose the greater threat to the lower respiratory tract.

The problems in learning the effects of particulates are further complicated by nonuniform methods of measurement. The two most widely used techniques, the high volume (HV) method and a class of smoke filter methods, measure different properties of the particulate complex.

The HV method, which is generally used in the US, employs a device that circulates large volumes of air through a filter. The weight of the particulates trapped on the filter is divided by the volume of the air sample and is reported in $\mu g/m^3$. The larger particles, of less importance to the lower respiratory tract, provide a disproportionately large contribution to the measurement.

When smoke filter methods are used, air is drawn through a filter paper and the density of the resulting stain is assessed by various techniques. These methods include the smoke shade method, commonly used in Great Britain, and the coefficient of haze (COH) method. The British smoke shade (BS) measurements are converted to an equivalent mass basis and expressed as $\mu g/m^3$, while the COH measurements are expressed in terms of optical density as COH units per 1000 linear feet of air.

The HV and smoke filter methods measure different attributes of particulate pollution; the measurements are not comparable. There have been many studies of the relationships between them, as summarized in Chapter 2 of (12). However, as is emphasized in (12), these relationships are empirical, and vary with the particular time and place of observation.

The results of controlled animal and human exposures to particulates, sulfur dioxide, sulfuric acid mist, and other sulfates are reviewed in [(7), Vol. 8, (8, 9, 13), and (14), pp. 175–225].

Photochemical Oxidants and Nitrogen Oxides

Photochemical oxidants are produced by nitrogen oxides, hydrocarbons, and solar radiation in a complex reaction. Combustion of fossil fuels and motor vehicle emissions provide major sources for the reactants. Ozone is generally the principal component and the one believed to be the most irritating to the respiratory tract. Also present but not usually measured are peroxyacetyl nitrate, acrolein, peroxybenzoyl nitrates, and aldehydes. Apart from NO_2, little is known about the respiratory effects of nitrogen oxides.

The problems in evaluating the effects of oxidants and nitrogen oxides have been discussed elsewhere (5–9, 15–18). One problem is that hydrocar-

bons from natural sources can react with ozone in the upper atmosphere to produce high ambient levels of oxidant. Another is that oxidants often occur simultaneously with very high temperatures, which can themselves aggravate disease and hasten death.

Like the particulate complex, oxidants and NO_2 present measurement difficulties. There has been concern (19) about the reliability and accuracy of the potassium iodide method of measuring total oxidant, which was widely used prior to 1975. In particular, reports using such measurements probably underestimate the actual oxidant levels. Similarly, serious error has been found in the Jacobs-Hochheiser method for measuring NO_2 [(13), pp. 317–44], a fact that compromises the utility of reports based on this procedure. Detailed discussions of current measurement methods for oxidants and NO_2 are contained in (15, 17) and (13, 16, 18), respectively.

There is no question that accidental exposures to high (greater than 150 to 200 ppm) levels of NO_2 can be fatal. Nevertheless, epidemiological studies have not shown a relationship between excess mortality and increased ambient NO_2 or oxidant levels, after adjusting for temperature. Moreover, little is known about the effects of chronic exposure to these pollutants. The difficulties in trying to provide such information are described in the next section.

THE PRESENT: WHAT IS THE EVIDENCE?

Detailed surveys of the health effects of selected air pollutants have been presented in US air quality criteria documents (2, 3, 14–16), which are periodically revised by the US Environmental Protection Agency. Comprehensive reports on the effects of certain air pollutants have also been published under the auspices of the National Academy of Sciences (5, 6, 13, 17, 18) and by the World Health Organization (7). In addition a number of investigators (8–12, 20–27) have published condensed and informative reviews of the field.

I make no attempt to duplicate the detail and scope of these surveys. Instead, I examine the findings of a small and arbitrary sample of studies concerning air pollution effects on respiratory health. Particular attention is paid to the quality of the data, to the methods of analysis, and to the implications of these factors for a study's utility in establishing standards. I argue that although some investigations provide strong evidence for adverse effects, many have serious weaknesses, and very few have any utility for estimating exposure-response relationships. Indeed, most of these studies were never intended to provide the detailed quantitative information that is needed to establish a reliable basis for setting standards.

Respiratory Mortality

SHORT-TERM EFFECTS The strongest evidence against ambient air pollution as a threat to health is provided by a series of acute episodes in the Meuse Valley in 1930 (28), in Donora in 1948 (29), in London in 1952 and 1962 (30, 31), and in New York in 1953 and 1962 (32, 33). These episodes, each involving several days of extremely high levels of sulfur oxide/particulate pollution, were marked by substantial increases in daily mortality. Although healthy persons were affected, the greatest toll occurred among those with preexisting respiratory and cardiac disease. No single pollutant could be incriminated.

Excess deaths were estimated as the difference between observed and expected as computed either from mortality during the same period in other years, from mortality during the previous or subsequent week, or from moving averages. The greatest estimated excess of approximately 4000 deaths occurred during the London fog of 1952. At this time the maximum 24 hour averages for SO_2 and particulates were estimated at 3830 $\mu g/m^3$ and 4460 $\mu g/m^3$(BS) (12). The subsequent London episode in December 1962 was characterized by greatly reduced air pollution and mortality. Part of the decreased mortality could be due to greater protective measures taken by the sick and elderly.

Approximately 20 deaths in a population of 13,000 were attributed to sulfur oxide/particulate pollution in Donora, Pennsylvania, with an estimated 6000 people suffering less serious effects. An investigation of a sample of this community nine years later showed that those affected by the episode had higher mortality rates and greater prevalence of respiratory disease in the interim than did those who were unaffected (34). This suggests either that acute exposures initiate enduring harmful effects, or that people who respond to acute exposures are already weakened and are thus more vulnerable to subsequent disease.

The Clean Air Acts of England in 1956 and of the US from 1963 to 1970 have been followed by the virtual elimination of dramatic episodes of high sulfur oxide/particulate pollution associated with increased mortality. This is indirect evidence in favor of a causal role for these pollutants.

The excess mortality observed in past episodes has prompted a number of studies on possible associations between temporal fluctuations in mortality and in sulfur oxide/particulate pollution. There have been several recent and comprehensive reviews (8, 9, 12, 14, 24) of these investigations. Here they are discussed only briefly.

The sensitivity of such studies depends on a number of factors, including the size of the study population and the variability in pollutant levels to which the population is exposed. Thus, most of the investigations have

taken place in large industrialized cities such as London (35–38), New York (39–44), and Tokyo (45), although there have been others in smaller cities (e.g. 14, pp. 263–309) and (46, 47). As a group, these studies persistently show a pattern of increased mortality on days or weeks of increased sulfur oxide/particulate pollution; however, there are several reasons why the results must be interpreted cautiously.

1. Influenza epidemics and temperature extremes can have a much greater effect on mortality than do moderate variations in air pollution. Other factors such as season and holiday weekends also influence mortality. If some of these factors are correlated with pollutant levels, then failure to control them adequately can either mask a real pollutant association or produce a spurious one. It is unlikely that air pollution is consistently correlated with these factors in all of the circumstances studied. Thus, the consistency of the findings relating air pollution peaks to mortality provides some evidence for causation. Nevertheless, the data do not support detailed quantitative interpretation. Regression coefficients and other measures of association are sensitive to the level of adjustment of confounding factors. Consequently, unless a study controls the above factors, it has little utility for estimating quantitative exposure-response relationships.

2. The accuracy of the measured pollutant levels as estimates of exposure is questionable. The pollution monitoring stations used in these studies typically were located on a very coarse grid over the area inhabited by the study population. The concentrations of SO_2 and particulates are dependent upon wind speed and direction and can vary appreciably over small areas. Further, those who by virtue of age or preexisting disease are at risk of death are apt to spend most of their time indoors. Thus density of cigarette smoke, type of heating and cooking fuel, and other determinants of indoor air quality may have more relevance to mortality than do moderate variations in outdoor levels as measured several kilometers away.

3. There is undoubtedly a variable lag time between a stressful event, such as an extreme of heat or air pollution, and the resulting deaths. This problem has been addressed by some investigators (42, 45); but without prior knowledge of the distribution of lag times, a satisfactory solution is elusive. The inability to deal adequately with this variability makes a study less likely to detect a statistical association, if it exists, between given pollution levels and mortality.

4. Findings at one time and place are not easily generalized to other circumstances. The geographical and temporal variability of sulfur oxide/particulate pollution in such characteristics as chemical composition and particle size distribution has already been stressed. Another barrier to generalization is the variability in characteristics such as size, susceptibility, exposure, etc of the sick and elderly subpopulation at risk.

The above difficulties make it impossible to determine from existing data general minimal levels of sulfur oxides and particulates at which excess deaths can be expected to occur. However, some order of magnitude estimates are necessary for control purposes. Based on data from New York and London (e.g. 36–38) it has been estimated [(7) Vol. 8, p. 90; (12), p. 656] that deaths are likely to increase when 24 hr averages of SO_2 and particulates exceed 500–700 $\mu g/m^3$ and 500 to 750 $\mu g/m^3$ (BS), respectively. The uncertainty of these estimates should be emphasized whenever they are quoted.

Perhaps the greatest limitation to further study of concommitant daily fluctuations in mortality and air pollution is the sizable decrease in pollution levels in the US and Western Europe following Clean Air legislation. This decrease means that a relatively weak signal emitted by current milder pollutant fluctuations is likely to be swamped by random and nonrandom variations in daily deaths.

LONG-TERM EFFECTS In evaluating the effects of air pollution, an important question is whether chronic exposure to elevated pollutant levels increases the chance of respiratory disease. Many workers have investigated this question by examining geographic differences in mortality rates due to bronchitis, emphysema, lung cancer, and other chronic respiratory diseases (cf, for example, 48–56). I do not discuss these studies individually. Instead, I summarize their general findings and point out some difficulties in interpreting these findings. The studies differ in the sophistication and care with which the statistical analysis is conducted (e.g., some control for smoking and occupational mix); however, all are subject to the inherent difficulties of not being able to control for all factors hypothesized to affect mortality across different areas. The reader interested in more details than are presented here will find them in (7–9, 12–14, 21–24).

The studies cited above have typically compared the mortality experience of residents in heavily polluted areas with that of residents in less polluted areas. They have shown a fairly consistent pattern of association between residence in a ...s of heavy air pollution and respiratory mortality. However, the assignment of an etiologic role for air pollution on the basis of these data is fraught with difficulties. Some of these difficulties are succinctly described in the following excerpt (8):

> Differences in mortality rates among geographic units cannot be attributed to differences in degrees of air pollution unless data on other determinants of geographic differences in mortality are taken into account. In many studies, information on these contributors to mortality is lacking or difficult to obtain. Thus, important factors such as smoking

habits, socioeconomic status, length of residence in the geographic unit, occupation, pre-existing disease, ethnic background, and diagnostic accuracy in filling out death certificates may significantly influence the reported mortality rate in each area.

In general, the designs of the studies cited above permitted little or no control for these important determinants of respiratory-related mortality. Hence, it is quite plausible that consistent confounding due to these factors may explain the consistency of the associations found. For example, people with lower socioeconomic status (SES) tend to smoke more cigarettes (56a) and live in more polluted areas than do those with higher status. Thus, cigarette smoking and SES could follow an air pollution gradient throughout most of the geogaphical areas studied. Further, because heavily industrialized areas are often heavily polluted as well, occupation among males may well be consistently correlated with residence in a dirty area.

Because air pollution measurements were not available during the lifetimes of those who died, these studies cannot provide exposure-response information. They have served a useful purpose in demonstrating geographical differences in mortality, but their limitations, together with those of the short-term mortality studies, imply that we must look beyond mortality to more sensitive measures, such as morbidity and decreased pulmonary function, for evidence on which to base sound air pollution control strategies.

Respiratory Morbidity

When the end point of interest is respiratory damage among the living, it is possible to study the effects of air quality on an individual and not on an aggregate or population level. This feature of morbidity studies permits more accurate estimates of exposure and better control of intervening variables than is usually possible when examining mortality.

SHORT-TERM EFFECTS Studies comparing temporal changes in respiratory status with concommitant pollution fluctuations are more sensitive indicators than are the corresponding mortality studies. Nevertheless, the four problems associated with studies of acute mortality effects—confounding by weather and season, inaccuracy of exposure estimates, unknown lags, and specialized pollution or population at risk—must also be addressed in acute morbidity studies. Reviews and critiques of selected short-term morbidity studies are presented in Tables 2 to 4. Those in Table 2 compare daily or weekly symptom reports with pollution variation. In addition to the above problems these studies are vulnerable to the vagaries of self-assessed symptom reporting and, unless the subjects are blind to the study's goals, to the possibility of reporting bias.

Table 3 describes studies of various measures of pulmonary function, as related to temporal changes in pollution. There are relatively few of these

studies because repeated pulmonary function tests are costly to perform and are subject to large errors due to variations in the performances of subject, machine, and technician.

The studies in Table 4 examine hospital or clinic visits vs temporal changes in air quality. The population served by the health facility is assumed to remain stable in size over the study period. Since influenza epidemics, season, and temperature are apt to be strongly correlated both with visits and pollution, these factors must be controlled if reliable information is to be gained.

All short-term morbidity studies share an important advantage: the study population can serve as its own control. The studies in Tables 2 and 3 have the additional asset that each individual can serve as his own control, with his own days or weeks of morbidity compared only to his own periods in good health. This approach, which avoids the obfuscation of interpersonal variability, has received too little attention. It will become increasingly useful as personalized exposure estimates become feasible.

LONG-TERM EFFECTS Some of the many studies attempting to determine the respiratory effects of chronic pollutant exposure are summarized in Table 5. Chronic respiratory disease is usually assessed by a questionnaire developed by the British Medical Research Council, administered either by mail or by personal interview. Its use facilitates reproducibility and comparability of results.

Although some investigators have tried to control for smoking and occupation, the cross-sectional studies of geographical differences in morbidity shown in Table 5 suffer from many of the severe limitations affecting the chronic mortality studies. There is little data on past exposures, and little or no control for selective migration in and out of polluted areas, or for important intervening variables. The cohort studies of temporal changes in respiratory morbidity within a single population, although expensive and time-consuming, provide the best tool for elucidating chronic effects.

The studies in Tables 2 to 5 were rated for their utility in estimating exposure-response relationships according to the following criteria:

1. Little or no utility describes those studies dealing only with qualitative or extremely crude quantitative estimates of exposure, or which suffer from severe limitations in design or analysis.
2. Moderate utility describes those whose estimates of exposure vs effect are limited by difficulties in assessing either exposure of effect, or in controlling for important intervening variables.
3. Substantial utility describes those with reliable exposure and effect estimates that are marred neither by major methodological flaws nor by inadequate control of important variables.

Table 2 Selected studies of short-term effects: respiratory symptom diaries

Description of study	Pollutants measured	Analysis and findings	Comments
Schoettlin & Landau (57).[a] Daily asthma attacks among 137 asthmatics in Los Angeles area, Sept. to Dec. 1956.	Oxidants; particulates (HV); carbon monoxide. No information on methods, location, or timing of pollution monitoring.	Simple correlation coefficients calculated between daily attack rate and pollutants, temperature and relative humidity. Correlation coefficients were not significant for particulates and CO. Multiple correlation coefficient relating attacks to oxidant, temp., and humidity was low. When oxidant exceeded .25 ppm, the mean number of subjects with attacks was significantly greater than when it did not, indicating that high levels may be hazardous.	No information on missing attack data, medication use, pollen counts. No adjustment for temperature, humidity, or serial correlation of attacks. No stratification on age or race.[c, d]
Zeidberg et al (58).[a] Daily asthma attacks among 49 adult and 34 juvenile asthmatics in Nashville, TN, July 14, 1958 to July 12, 1959.	SO_2, particulates (HV, COH) measured at several monitors on a fine grid over study area.	Cross-sectional analysis. Crude annual attack rates calculated for each of three categories of asthmatics, classified according to annual geometric mean sulfation rate at monitoring station nearest to home. Attack rates follow a pollution gradient for adults but not for children; however, no statistical tests for trend were reported. Comparison of attack rates when SO_2 levels were above and below their median yielded no significant differences. Pollen levels and wind velocity were uncorrelated with attacks. Relationship between particulates and attacks was not reported.	Cross-sectional analysis used does not account for demographic and other differences among asthmatics in the three pollution categories. Attack data missing for 10% of all person-days of observation. Analysis did not use data efficiently. Pollution levels aggregated arbitrarily. No data on medication use.[c, d]
Cohen et al (59).[a] Daily asthma attacks among 20 New Cumberland, WV asthmatics residing within ½ mile of a coal-fueled power plant during December 1969 to June 1970.	Particulates (HV, COH); SO_2, sulfates, nitrates as measured at 3 monitors. Distance of asthmatics from monitors unspecified.	Multiple linear regression of daily attack rate against pollution and weather variables. Wind speed, humidity, and barometric pressure were each uncorrelated with attack rate. After adjustment for temperature, each pollutant was positively associated with attack rate. After adjustment for temperature and any one pollutant, none of the others explained a significant amount of attack rate variation.	No information on missing attack data, medication use, pollen counts. No adjustment for serial correlation of attacks. Results not easily generalized, as pollutant mix may be unique to area. Some reported attacks were confirmed by a physician.[c]
Whittemore & Korn (60).[b] Daily asthma attacks	Oxidants, particulates (HV) monitored within	A separate multiple logistic regression was used for each subject's attack data. Independent variables	Analysis did not use data on medication use. No data on

among 443 asthmatics in the Los Angeles area during 34 week periods in the years 1972 to 1975.	approximately 3 mi of subjects' homes.	were oxidant level, particulate level, temperature, humidity, wind speed, day of week, presence or absence of attack on preceding day and day of study. Average regression coefficients for both pollutants were significantly positive. There were no significant differences in response to pollution among subjects when classified according to age, sex, or self-assessed asthma type.	pollen counts. Potential bias of missing attack data is minimized by individual regressions.[c, d]
Hammer et al (61).[b] Daily symptom reporting by student nurses working and residing at two Los Angeles hospitals. Oct. 1961 to June 1964.	Daily maximum of hourly measurements for oxidant, CO, NO_2 as monitored at a single station within 2 mi of hospitals.	Respiratory symptoms were cough and chest discomfort. The symptom rate for a day was defined as the number of students reporting the symptom divided by the number completing a diary on that day. For each symptom the authors assumed a threshold level below which the symptom rate is independent of oxidant. Estimates and confidence intervals for these levels were obtained. In addition, the average daily symptom rate was computed for 8 categories of oxidant level. Although not verified by statistical tests, the rates for both cough and chest discomfort were increased at levels greater than 0.30 ppm.	No adjustment for temperature, humidity, CO or NO_2. The authors report that there is no relationship between symptoms and either temperature, CO or NO_2, but give no supporting evidence. No adjustment for missing data. No examination of validity of threshold assumption.[c, d]
Lawther et al (62).[b] Daily changes in condition of 19 to 250 bronchitic patients in London and other British cities during the winters of 1955–1956, 1957–1958, 1959–1960, 1964–1965.	24 hr average levels of SO_2 and particulates (BS). Number of stations per city varied from 1 to 7 depending on year and location of study.	Only descriptive, graphical methods used. Four possible categories of daily condition were given arbitrary numerical scores. Daily scores were averaged over those reporting. The mean daily scores, as well as the fraction of those reporting their condition to be worse than the day before, were plotted against time. Plots of daily pollutant levels were shown on same graphs as the illness indices. Illness and pollution peaks tended to coincide. The authors judged that 500 $\mu g/m^3$ of SO_2 and 250 $\mu g/m^3$ of particulates (BS) are minimal levels leading to increased illness response.	No information on subjects' knowledge of pollution-related study goals. No adjustment for temperature, humidity, missing data or serial correlation in morbidity indices. Assessment of minimal pollutant levels at which effects were seen is somewhat subjective in the absence of formal analysis of random variation in data.[c]

[a] Little or no utility for estimating exposure-response relationships.
[b] Limited utility for estimating exposure-response relationships.
[c] Daily morbidity status was self-assessed.
[d] To reduce reporting bias, subjects were not informed of pollution-related study goals.

Table 3 Selected studies of short-term effects: pulmonary function

Description of study	Pollutants measured	Analysis and findings	Comments
Motley et al (63).[a] Pulmonary function tests in 66 subjects (of whom 40 had emphysema) before and after stays in filtered rooms for periods of 2 to 4, 18 to 20, or 40 to 90 hr. Study took place in Los Angeles during 3½ yr period beginning 1956.	Air quality during the 3 to 4 days prior to filtered exposures was classified as clear or smoggy on the basis of pollution values at nearby station. Smog consisted of oxidant, NO_2, CO, SO_2.	Each subject served as his own control. No consistent differences were noted when prior air was clear, when filtered exposures were less than 40 hr, or among normal subjects. Consistent differences were noted during smog when emphysematic subjects breathed filtered air for at least 40 hr. These differences were displayed graphically but not subjected to statistical testing.	Although possible differences in temperature and humidity were not controlled, this study provides evidence of transient decreased pulmonary function in emphysematic subjects due to smog. No specific pollutants could be incriminated.
Wayne et al (64).[a] Performance of long distance runners in 21 student meets at a Los Angeles high school from 1959 to 1964.	Oxidants, nitrogen oxides, CO, particulates (HV), measured at station 2 mi NW of high school.	Univariate linear regressions of fraction of runners who failed to improve their previous performance vs hourly concentration of each pollutant. Strong associations found for oxidant and particulates.	No control for temperature, humidity, or correlation of oxidants and particulates.
Lawther et al (65, 66).[b] Pulmonary function measurements on 4 normal male nonsmokers in London on each working day during 5 yr period from 1960 to 1965.	Particulates (BS), SO_2 measured at testing [illegible]b.	I. For each individual, mean values of FEV_1,[c] FVC,[d] MMF[e] were computed for 6 ranges of particulates and 6 ranges of SO_2. χ^2 tests were used. In 3 of the 4 subjects MMF was consistently related to both pollutants. In 1 of these 3 subjects, FEV_1 also followed a gradient for both pollutants. There were no consistent relationships between FVC and pollution. II. Multiple linear regression of PEF[f] values averaged over all 4 subjects vs log SO_2, log particulates, temperature, and relative humidity. Mean PEF values increased with time and temperature and decreased with SO_2 levels.	I. Large amount of missing pulmonary function data. Univariate analyses of FEV_1, FVC, and MMF vs pollutants did not control for weather, respiratory infections or other pollutants. Pollutant levels were arbitrarily grouped into categories. I and II. It is not clear why individual multiple linear regressions were not used for each subject and for each measure of lung function.
Lebowitz et al (67).[a] Pulmonary function tests on 6 to 12 yr old children	Particulates (HV), sulfates, temperature, and humidity were com-	Children: no significant differences between preexercise and postexercise pulmonary function measurements for indoor group. Decreased post-	Age, height, and weight were controlled by converting lung function measurements to per-

before and after lunch-exercise periods indoors in Tucson (30 boys); outdoors in Tucson (60 children); outdoors in a copper smelting town in Arizona (17 children). Pulmonary function tests on 2 groups (9 adolescents and 10 adults) before and after walking or running outdoors in Tucson. Testing performed on unspecified dates, approximately 1972.	bined into a single additive index. Monitoring stations were within .25 mile of testing sites for children, but more than 3 mi from testing sites for adolescents and adults.	exercise measurements among those children in outdoor Tucson group who exercised on 2 high pollution days, but not for the remaining children who exercised on 2 low pollution days. Children in copper smelting town showed a significantly greater postexercise decrease in FEV/FVC and MMF on high pollution days than on low pollution days. Adolescents: mean FEV_1 and FVC were significantly decreased after their 20 mi walk. Adults: no significant changes after exercise.	centage of predicted as calculated by specified formulae. No explanation of statistical methods. Effects of temperature, humidity, and pollutants cannot be separated. Effects noted among the outdoor Tucson group are confounded by the differences in children exercising on high and low pollution days.
Stebbings et al (68).[b] Daily pulmonary function measurements of 270 children in fourth to sixth grades of 6 schools during and after period of high pollution (November 21–26, 1975) in Pittsburgh. Two schools (approx. 80 children) were in control areas. The goal was to see if the measurements of children in polluted areas improved over the study period while those in the control areas remained the same.	Particulates (COH), SO_2 measured at stations within 3 mi of schools.	Mean $FEV_{.75}$[c] and FVC[d] were computed for each day and each school, adjusting for the children untested on that day. There were no temporal increases in adjusted mean measurements for children in polluted areas.	Method of adjustment for children not tested on a given day is not clear.

[a] Little or no utility for estimating exposure-response relationships.
[b] Limited utility for estimating exposure-response relationships.
[c] FEV_x = forced expiratory volume in x seconds.
[d] Forced vital capacity.
[e] Maximum midexpiratory flow.
[f] Peak expiratory flow.

Table 4 Selected studies of short-term effects: hospital/clinic visits

Description of study	Pollutants measured	Analysis and findings	Comments
Durham (69).[a] Clinic visits for respiratory illness among students at 7 California universities during 1970 to 1971 academic year.	Oxidant, NO_2, SO_2, NO, CO, particulates, hydrocarbons monitored within approximately 5 mi of school.	Simple correlation coefficients were computed between specific upper respiratory symptoms and daily pollutant levels, as measured 0 to 7 d before symptom was first noticed. Factor analysis was used to control for weather. Visits for pharyngitis, bronchitis, tonsillitis, and colds were associated with oxidant, SO_2 and NO_2 for schools near Los Angeles, but not for schools near San Francisco. Analysis of sub-populations indicated that male smokers were particularly affected by pollution.	Thorough study of associations between upper respiratory symptoms and pollution. It is not clear how well seasonal and day-of-week variations were controlled. As no pollutant levels were specified, exposure-response relationships cannot be inferred.
Fishelson & Graves (70).[b] Emergency room visits for respiratory disease in Chicago's Cook County Hospital on 81 Tuesdays from mid-Sept. 1971 to end of March 1973.	SO_2, particulates (COH). Measurements averaged over 5 stations surrounding hospital.	Multiple linear regressions of number of respiratory admissions among males and females vs daily pollutant levels (with lags of 0 and 1 d), temperature, humidity and an indicator for holidays. A small positive association was found for SO_2 but not for particulates.	No control for influenza epidemics or season. A "lagged dependent variable" was included in some regressions as a surrogate for unspecified intervening factors; its interpretation is not clear.
Levy et al (71).[a] Hospital admissions for respiratory disease in Hamilton, Ontario, July 1, 1970 to June 30, 1971.	Sulfur oxides, particulates (COH), oxidants, CO, nitrogen oxides, hydrocarbons, monitored at one station in heavily polluted part of city.	Univariate linear regressions between total weekly admissions at each of 4 hospitals and average monthly pollutant levels. Associations found with SO_2 and with particulates. Strength of association varied inversely with distance of hospital from monitoring station. No associations found with remaining pollutants, pollen count, or humidity. Authors state that associations of admissions with SO_2 and with particulates persisted when temperature was included in regressions, but do not present this analysis.	This paper is missing important details on independent variables used in the regressions. No adjustment for variations due to season or holiday weekends. Authors report no influenza epidemics during study. Aggregating data into weekly and monthly averages is insensitive.

Goldstein & Block (72).[a] Emergency room visits for asthma in Harlem and Brooklyn, New York, Sept. to Dec. 1970 and Sept. to Dec. 1971.	SO_2, smokeshade (COH) as monitored within approximately 3 mi of hospitals.	Multiple linear regression of daily asthma visits vs daily average SO_2 level and daily average temperature. Positive association with SO_2 noted for Brooklyn but not for Harlem.	The authors believe that lack of adjustment for season, weekdays, holidays is not likely to explain anomalous results. They conjecture that SO_2 may be a surrogate for an asthma-inducing agent present in Brooklyn but not Harlem. No information on weather variables. Particulates and CO, although high during episode, were not measured.
Chiaramonte et al (73).[a] Daily emergency room visits for respiratory disease by children to a Brooklyn hospital for 3 wk in Nov. 1966, including 1 wk of very high pollution.	SO_2, as monitored approxim. ·ely 5 mi from hospital. 5 d of missing data.	Week of high pollution characterized by marked increase in visits over those observed during 2 control weeks. Statistical methods not explained.	
Ipsen et al (74).[a] I. Weekly clinic visits amorg employees of two companies in Philadelphia for 165 wk, Oct. 1960 to Sept. 1963. II. Daily employee absenteeism in one company in Philadelphia for 850 days, Sept. 1961 to Dec. 1963.	Particulates, smokeshade, sulfates, SO_2, NO. No information on number and location of stations.	I. Multiple linear regression. Dependent variable: total weekly visits divided by average size of quarterly working force. Independent variables: average weekly levels of pollutants (excluding SO_2 and NO), temperature, humidity, wind speed and direction, precipitation. No consistent associations with pollution after adjustment for meteorology. II. Univariate linear regressions of daily incidence (number of first-day absences) and of daily prevalence (number of absences) vs particulates, temperature, relative humidity, and wind speed. No consistent pollutant associations noted.	I. High intercorrelation of pollutants could account for lack of association noted in multiple regressions, but no information on these intercorrelations given. Aggregation of data by weeks is insensitive. II. Extensive use of descriptive statistics. Not all statistical approaches are clearly explained. No apparent adjustment for intercorrelation of pollution and weather variables.

[a] Little or no utility for estimating exposure-response relationships.
[b] Limited utility for estimating exposure-response relationships.

Few of the studies reviewed have moderate utility for estimating dose-response, and none of them has substantial utility for this purpose. This is not a sweeping denial of their value, because most were designed to produce only qualitative information. They have yielded important insights; however, now more is needed.

THE FUTURE: WHAT MUST BE DONE?

Are the US air quality standards adequate for protecting the public health? Are they too stringent? Resources for the control of air pollution are not infinite. At some point, a greater improvement in health and welfare can be expected from a more viable economy than from a reduction in pollution. Clearly, the evidence reviewed in Tables 2 through 5 does not provide an adequate basis for determining that point. It is essential that we improve the technical data base used to set standards. Improvements are needed in the assessment of exposure, of disease, and of the relationship between the two.

Pollution Exposure Assessment

Uncertainty about actual exposures to the respiratory tract is a great weakness of existing studies. This uncertainty is typically disregarded when results are reported. For example, when disease is regressed on pollution measurements, the analysis often acknowledges only the randomness of the disease variable, and not the large uncertainties in the exposure estimates. However, nonsystematic error in an exposure variable can bias the corresponding estimated regression coefficient toward zero (98, p. 376). This bias, whose magnitude depends upon the size of the error and on other variables in the regression, increases the likelihood of false negative studies.

While exposure uncertainties can never be eliminated entirely, there are several ways in which they can be reduced in studies of short-term effects on morbidity. Small, portable personal monitors may one day become practicable on the scale needed for epidemiological studies. Until then, study subjects' time could be classified into various spatio-temporal "bins," e.g. resting indoors in the evening, exercising outdoors, driving a car during rush-hour, etc. Concentrations of pollutants could be monitored over time for each of the bins, and an individual's exposure on any given day could be estimated as an average of such concentrations, weighted by the fraction of the day spent in each bin. Thus, proper weight could be assigned to pollutant levels indoors where most people, particularly the more vulnerable sick and elderly, spend the majority of their time.

Methods for differentiating particles chemically and for measuring those of a given size distribution need to be standarized and incorporated into all

Table 5 Selected studies of long-term effects

Description of study	Pollutants measured	Analysis and findings	Comments
Ferris et al (75, 76).[b, c] Survey of respiratory disease and pulmonary function among random sample of 1167 residents of Berlin, NH aged 25 to 74 in 1961, followed by repeat surveys of same sample in 1967 and 1973. Disease symptoms obtained by interviews using BMRC[e] questionnaire.	Particulates (HV), SO_2, SO_3, averaged over a 9-month period in 1961, a 22-month period from 1966 to 1967, and an unspecified period in 1973. The 3 mean particulate levels decreased with time, while the mean SO_2 levels increased.	Slightly lower prevalence of chronic respiratory disease and improved pulmonary function in 1967, when compared with 1961, after standardization for age, sex, and smoking habits. No statistical assessment of these changes. No differences in respiratory symptoms, chronic respiratory disease prevalence or pulmonary function between 1967 and 1973.	No adjustment for possible seasonal and weather differences among the three surveys. Problems of selective loss to follow-up could not be completely addressed. Decreases in particulates could reflect reduction in particles of nonrespirable size. Generalization limited by possible uniqueness of pollutant mix in a pulp mill community.
Winkelstein & Kantor (77).[a, d] Prevalence of cough with phlegm as reported by 842 white women, in Buffalo, NY, 1961 to 1963, using mailed questionnaire.	SO_2, particulates (HV) based on average levels over period of 1961 to 1963. Distance of stations from subjects' homes not stated.	Subjects classified according to 4 categories of SO_2 and particulates. No consistent or statistically significant association between cough prevalence and either pollutant.	Arbitrary and inefficient grouping of pollution averages. Smoking stratified only as smoked/never smoked. Incomplete control for social status, migration.
Lambert & Reid (78).[a, d] Respiratory symptoms among 9975 British residents aged 35 to 64 during 1965, obtained by mailed BMRC questionnaire.	Index based on domestic coal consumption obtained in 1952 for 88% of areas studied; particulates (BS) and SO_2 obtained in 1965 for at most 30% of areas studied.	Age and smoking adjusted prevalence rates of persistent cough with phlegm follow a pollution gradient for each pollution index. Gradient more pronounced for smokers than for nonsmokers. No statistical analysis of trends.	No adjustment for occupation, social class, or change of residence.

Table 5 *(Continued)*

Description of study	Pollutants measured	Analysis and findings	Comments
Colley & Reid (79).[a, d] Respiratory symptoms and pulmonary function among 10,000 British and Welsh children from Sept. to Nov. 1966. Symptoms obtained by mailed questionnaire.	Crude estimates of winter mean SO_2 levels during 1966, 1967.	Chronic cough prevalence follows pollution gradient only for children in working class families. No statistical assessment of trends.	Pollution measurements inadequate. No adjustment for parental smoking or for cooking and heating fuel type.
Hrubec et al (80).[a, d] Survey of respiratory symptoms among 4377 pairs of US male twins and an additional 2364 unpaired twins aged 41 to 51 obtained by BMRC questionnaire administered by mail in 1968.	Emission estimates for 188 US metropolitan areas during period from 1965 to 1967 were used in diffusion model to obtain single measures of particulate, SO_2, and CO levels. These measures were combined into a single index for each ZIP code location. Pollution exposure scores were computed for each subject based on residence and employment history. An urbanization score was also assigned to each subject.	Two analyses were performed: 1. All subjects were treated as individuals and only one twin of each pair was included. Respiratory symptoms were associated with urbanization scores but not with pollution scores. 2. Only twin pairs concordant for smoking and discordant for pollution or urban scores were included. Respiratory symptoms were associated with neither urbanization nor pollution exposure scores.	Occupation and indoor exposures were not controlled in the analysis. Negative results may be due to low prevalence of chronic respiratory symptoms among men aged 41 to 51, or to inefficient statistical methods.

Shy et al (81, 82, 83).[a, d] I. Weekly pulmonary function measurements for 987 second grade children in 4 areas of Chattanooga, TN during Nov. 1968 and March 1969. II. Biweekly diaries of respiratory illness among families of above children from Nov. 1968 through April 1969. III. Survey of bronchitis, croup, and pneumonia among 1311 infants and 1906 first and second grade children in areas 1, 3, and 4 from July 1966 to June 1969 obtained by questionnaire mailed or brought home from school.	NO_2, particulates (HV, COH), sulfates, nitrates. High NO_2 in area 1; high particulates in area 2; moderate levels of NO_2 in area 3; low levels of all pollutants in area 4.	I. Height and sex-adjusted $FEV_{.5}$[f] was significantly lower in high NO_2 area 1 than in areas 3 and 4. However, there was no NO_2 gradient for individual schools within the high NO_2 area. II. Illness rates significantly higher in high NO_2 area than in areas 3 and 4 for the children, their siblings, and parents. These differences could not be explained by differences in family size, economic level, or prevalence of chronic respiratory conditions. No correlation between illness rates among children and parental smoking. III. Ridit analysis was performed on the proportions of children reporting one or more illness episodes. Bronchitis rates were significantly elevated for school children exposed to high NO_2 for 2 or 3 yr, but not for those exposed for 1 yr or for infants. Bronchitis rates followed an NO_2 gradient only for children exposed for 3 yr. No significant area differences in rates for croup or pneumonia.	I. The authors found no differences in parental smoking and social class between areas 1, 3, and 4, and so did not control for these variables. No adjustment for indoor fuel type. Lung function technicians were rotated between areas. II. Parental illness rates were not adjusted for differences in age and smoking status. No adjustment for home heating and cooking fuels. III. No adjustment for indoor pollution levels at home. I–III. High NO_2 area also had higher sulfates and nitrates than did other areas. Jacob-Hochheiser method for analyzing NO_2 later found to be in error. No information on area differences in retirement or in transfers to inside assignments because of respiratory problems. Results not easily generalized because of possible self-selection by men more tolerant of automobile exhaust.
Speizer & Ferris (84, 85).[a, d] Survey of respiratory symptoms and pulmonary function in 128 central city and 140 suburban Boston policemen with outdoor duties during winter of 1969 to 1970 from BMRC questionnaire administered by a trained physician interviewer.	SO_2, NO_2, CO, hydrocarbons, lead, measured during study by portable monitors on the streets. Differences in pollutant levels between suburban and central city areas are not specified.	Nonsmokers and smokers (but not exsmokers) from the central city group had slight but nonsignificant excess in symptom prevalence when compared to suburban group. Methods used to analyze symptom prevalence are not described. Multiple linear regression of FEV_1[f] against age, height, smoking, and years of traffic exposure indicated that FEV_1 is not associated with traffic exposure.	

Table 5 *(Continued)*

Description of study	Pollutants measured	Analysis and findings	Comments
Cohen et al (86).[b, d] Respiratory symptoms and lung function tests among 441 nonsmoking Seventh Day Adventists in Los Angeles and San Diego, 1970. Respiratory symptoms obtained from BMRC questionnaire administered by a single interviewer.	Particulates (HV), NO_2, oxidant, SO_2, nitrates, and sulfates. Distance of stations from subjects' homes not stated. Average annual pollutant levels for both cities were low and comparable, but daily oxidant peaks were greater in Los Angeles.	Analysis of variance of spirometric and flow volume parameters vs city of residence, age, height, and social status was performed for each sex. No significant differences between cities for any of the pulmonary function parameters tested. No significant intercity differences in symptom prevalence after control for age and sex.	Recent migrants were excluded from study. Low and similar pollutant levels throughout the subjects' lifetimes could explain negative results.
Aubry et al (87).[b, d] Survey of respiratory symptoms and lung function among 237 men and 244 women aged 45 to 64 in 3 communities in Montreal area during 1972 to 1973. Respiratory symptoms obtained by BMRC questionnaire. No details about number of interviewers or whether they were rotated among communities.	Particulates (HV, COH), dust fall, SO_2, SO_3, averaged over period 1970 to 1974. High SO_2 in community 1; high particulates in community 2; low particulates and SO_2 in community 3.	Discriminant analyses performed for community 1 vs community 2, and for communities 1 and 2 vs community 3. Independent variables were age, smoking habits, coded respiratory symptoms, and pulmonary function. No significant intercommunity differences in male respiratory symptoms or lung function. Prevalence of cough and phlegm among women was significantly higher in communities 1 and 2 than in community 3.	No adjustment for social class, occupation, change of residence, or indoor fuel type. Sensitivity of conclusions to departures from assumptions of discriminant analysis is not addressed. Small sample sizes might explain negative results for males.

Douglas et al (88, 89, 90).[a, c] I. Respiratory symptoms in 3131 children born in Great Britain in 1946 who resided since birth in areas of high, medium, low, or very low pollution. Illness information obtained by interview with mothers at ages 2 and 4 yr, and during examinations by school doctors at ages 5, 6, 7, 11 and 15. Hospital admissions recorded. Special absence records kept at school from ages 6.5 to 10.5 yr. II. Survey of prevalence of cough in winter among 3899 20-yr-old members of above cohort. Survey repeated at age 25.	Annual domestic coal consumption in region of residence during 1952 was used as an index of air pollution.	I. Upper respiratory infections not related to air pollution, but frequency and severity of lower respiratory tract infections increased significantly with pollution. This association held for both sexes, for all social classes, and at each age examined. II. Multiple linear regression of winter cough prevalence at age 20 vs smoking habit, childhood chest illness, father's social class, and air pollution index yielded no significant association between cough and air pollution. Multiple logistic regression of cough prevalence at age 25 vs above factors yielded slightly stronger but still non-significant association with pollution.	I. No control for parental smoking or indoor fuel use. Study provides qualitative evidence that air pollution is related to lower respiratory disease in early childhood. Specific pollutants cannot be identified. II. 17% of those still living in UK at age 18 were lost to follow-up, and this group contained a disproportionate number of individuals from areas of high pollution. No control for parental smoking and indoor fuel use.

Table 5 *(Continued)*

Description of study	Pollutants measured	Analysis and findings	Comments
Lunn et al (91, 92).[b, d, e] Respiratory symptoms and pulmonary function among children in 4 areas of differing pollution in Sheffield, England. 819 children aged 5 and 1049 children aged 11 examined at school during summers from 1963 to 1965; 558 of those aged 5 reexamined 4 yr later in summers of 1967 to 1969.	Particulates (BS) and SO_2 measured from 1964 to 1968 at stations within 1 mi of schools. Particulates, and to a lesser extent SO_2, decreased over study period.	Children aged 5: significantly decreased prevalence of chronic upper respiratory tract infection, of history of 3 or more colds per year, and of history of chronic cough, pneumonia, or bronchitis in clean vs polluted areas. Four years later, no significant differences between areas were noted. Children aged 11: less respiratory morbidity and smaller differences between areas than exhibited by 5-yr-olds. No significant area differences in pulmonary function for any age group.	Social class and family size followed pollution gradient. However there were few consistent or significant relationships between respiratory symptoms and either social class or family size. Parental smoking, indoor fuel use, and loss to follow-up among 5-yr-olds were not addressed.
Holland et al (93).[a, d] Survey of peak expiratory flow rate (PEFR) in 10,971 school children aged 5, 11, and 14, in 4 areas of differing pollution in Kent, England during 1964 and 1965.	Mean particulate levels for each area during winter of 1966 to 1967 are presented, but their source is unspecified.	PEFR was adjusted for age, height, and weight in each age and sex group by a multiple linear regression equation. Analysis of variance of adjusted PEFR vs area, social class, number of siblings, and previous history of bronchitis or pneumonia yielded significant differences in PEFR among areas for all age-sex groups, with areas of low pollution having improved PEFR.	No control for parental smoking or indoor fuel use. Results provide qualitative evidence relating pollution to PEFR in children. Specific pollutants could not be identified.
Melia et al (94, 95, 96).[a, c, f] Respiratory symptoms and lung func-	NO_2 measured in kitchens, in children's bedrooms, and outside of	Children cross-classified by age, father's social class, and presence or absence of 1 or more respiratory symptoms. Log-linear models fitted separately for	Because of its conflicting and statistically weak results, study does not determine whether

tion among 4827 children aged 6 to 11 yr in England and Scotland from 1972 to 1977.	homes for 1 wk in winters. Mean NO_2 levels higher in kitchens and bedrooms of homes using gas as compared to electric cooking.	each sex and for urban and rural areas. According to this analysis, which did not control for parental smoking, gas cooking was significantly ($p < .05$) associated with respiratory illness only for boys in urban areas. These results also held after adjustment for heating fuel type and for outdoor levels of particulates and SO_2. Effects of gas cooking smaller in 1977 than in 1973. Multiple logistic regression of presence or absence of respiratory illness vs father's social class, age, sex, familial smoking, and NO_2 in kitchen or child's bedroom yielded marginally significant association between respiratory illness and NO_2 levels in bedroom. No relation between NO_2 levels in kitchen and respiratory illness in children, siblings, or parents, or between lung function and NO_2 levels in kitchen or bedroom.	indoor NO_2 levels are harmful to health.
Kerrebijn & Mourmans (97).[a, d] Respiratory symptoms and lung function obtained for 2380 fourth and fifth grade children in 2 areas of Westland, Holland during spring 1973. Symptoms obtained by questionnaire mailed to parents.	Winter and summer mean levels of particulates (BS) and SO_2 measured at 7 stations in area 1 (high pollution) and 1 station in area 2 (low pollution). Average distance of stations from schools not specified.	Children cross-classified by area and presence or absence of symptom for each of 13 symptoms. Only cough during day or night was more prevalent ($p = .05$ by Fisher's exact test) in area 1 than in area 2. Area 1 had no consistent excess of remaining symptoms. No area differences in lung function. Children in areas 1 and 2 comparable in social class and family size.	In view of multiple comparisons of symptoms and statically weak results, study provides no convincing evidence for pollution effect on respiratory status of fourth to fifth grade children. No information on rotation of technicians between areas. No control for parental smoking or indoor fuel type.

[a] Little or no utility for estimating exposure-response relationships.
[b] Limited utility for estimating exposure-response relationships.
[c] Cohort study.
[d] Cross-sectional study.
[e] British Medical Research Council.
[f] FEV_x = forced expiratory volume in x seconds.

monitoring systems. In addition, techniques for measuring other monitored pollutants should be standardized. Information on measurement and calibration methods, and on the distance between monitoring stations and populations at risk, should be included in the reports of all studies.

The difficulties of apportioning risk among highly correlated pollutants suggests that control efforts should be directed toward profiles of several pollutants.

Respiratory Disease Assessment

In their search for evidence against air pollution, epidemiologists are hampered by ignorance of the precise pathophysiological mechanisms by which airborne toxicants are likely to induce acute and chronic respiratory disease. Dialogue with toxicologists can stimulate animal and controlled human experiments, which in turn can provide information useful in the design of observational studies.

Apart from our need for more knowledge about disease mechanisms, there is need for improved measurement of respiratory damage. Subjective measures of acute morbidity, such as presence of cough, chest discomfort, or asthma, should have some objective confirmation, such as recorded times of medication use or verification by a physician.

The precision by which any lung function test can predict the development of disabling disease is unknown. Commonly used spirometry measurements, such as forced expiratory volume and peak expiratory flow rate, probably reflect disturbances in the large airways. Unfortunately, they are relatively insensitive to those changes in the small peripheral airways that may mark the start of chronic disease (12). Longitudinal studies show great variability in one person's pulmonary function measurements over time, as well as in rates of decline between people. The prognostic importance of this variability has not been adequately studied. Even in long-term studies the calculated individual rates of decline are not highly reliable. Better methods of analyzing this type of data are needed.

The questions of how many pulmonary function tests a subject should receive at one testing, and whether to take the mean or the maximum reading, are important. The procedure should be standardized (see 99). To insure the output of reliable data, studies must be designed to provide for instrument calibration between testings, and to adjust for measurement differences between instruments and between technicians.

Exposure-Response Assessment

Implicit in the US Clean Air Act is the assumption that no-effect levels of pollutants can be determined. However, the concept of such levels is a

politically attractive chimera. No-effect levels, be they positive or zero, must depend upon the individual, the weather, the pollutant mix, the disease, and many other variables. Even for particular values of all these variables, such levels are impossible to estimate with useful precision. Rather than waste effort debating the existence and values of no-effect levels we must face the possiblity of some risk at any positive level, and decide which risks are tolerable.

Exposure-response assessment suffers from a dearth of reliable evidence. The paucity of epidemiological data on respiratory effects at levels near the current standards has been stressed elsewhere (e.g. 12). Although the absence of reliable data supporting the relaxation of standards should receive equal emphasis, it does not. The insensitivity of existing studies to the effects of moderate levels of pollutants is poorly appreciated.

There are several sources of this insensitivity: (*a*) insufficient variability in exposures to pollutants, (*b*) large random errors in measuring exposure to pollutants, (*c*) inadequate control of confounding factors, (*d*) insufficient sample sizes, (*e*) the chance that reactions of sensitive subgroups will go unnoticed. Temporal studies of acute effects are further weakened by unknown lags between exposure and effect, while cross-sectional studies of chronic effects are muddied by migration in and out of geographical units.

Because of these limitations, negative results cannot be automatically interpreted as evidence of safety. At best, such results provide crude upper bounds for effects. At present the lack of documented evidence on adverse effects at levels slightly above the standards cannot be construed as evidence in favor of relaxing them. More sensitive studies are needed. What must be done to achieve them?

Recommendations

1. We must reduce exposure uncertainty with more accurate, better calibrated, standard measuring devices located close to the nose and mouth of the population at risk. The notion of parceling subjects' time into bins and monitoring the bins, described earlier in this section, deserves implementation in short-term morbidity studies.

2. We should abandon hope of elucidating chronic effects by studying current or former smokers. Cigarette smoking so dominates air pollution as a respiratory hazard that these people cannot provide information on chronic effects without precise control of such myriad smoking modifiers as duration, pattern, amount, depth of inhalation, and tar and nicotine content. The impracticality of doing this suggests that future chronic effects studies be restricted to life-long nonsmokers. Similar comments apply to strong occupational respiratory hazards.

For these reasons studies in children are uniquely valuable. Insults to the respiratory tract in childhood may be one of the important determinants of chronic respiratory disease in adulthood. To clarify this, cohorts of children whose exposures are being documented and who remain nonsmokers should be followed into adulthood for chronic disease. Unfortunately, the necessary restriction of study to nonsmokers precludes the investigation of possible interaction between cigarette smoke and air pollution in the induction of respiratory disability.

3. More thought must be given to study design. Due to the many limitations cited in the previous pages, further cross-sectional studies of chronic effects are not likely to be useful in determining standards. Long-term cohort studies of geographical differences in pulmonary function changes share some of these limitations and thus should be undertaken only with the greatest care. Current air quality monitoring and data storage and retrieval are sufficiently developed so that within the next few decades, national data banks on average air pollution levels by time and place of residence may be available. It may thus be feasible to conduct retrospective studies of lifetime exposures among nonsmoking, nonoccupationally exposed victims of chronic lung disease as compared with exposures among suitably chosen controls. As with all chronic effects studies, the sensitivity of these retrospective studies would be compromised by large errors in exposure estimates. Further, they would be subject to at least as many potential biases as are corresponding cohort studies. Nevertheless, because the frequency of chronic lung disease is low, the retrospective studies would be substantially cheaper and more efficient than the cohort studies.

Short-term studies of acute nonfatal events as they vary with pollution over time, while unable to answer the important questions concerning chronic effects, have the best prognosis for sensitivity, reliability, and feasibility. It is important that existing studies of this type be duplicated using improved design, exposure assessment techniques, and analysis.

4. Analysis of all studies can be improved. Future investigators should exploit recent statistical methods for controlling intervening variables and for increasing sensitivity. Tables 2 through 4 show that many studies failed to adjust for weather and other pollutants even when data on these variables were available. The sensitivity and validity of studies such as those in Tables 2 and 3 can be enhanced by relating disease to exposure on an individual rather than on an aggregate level. Finally, study plans should include more careful sample size calculations.

While implementation of the above recommendations will help to improve the epidemiological evidence upon which regulatory decisions are based, it is unrealistic to expect that "perfect" studies will some day be

possible. Exposure can never be known with complete accuracy, nor can confounding be completely controlled. These basic limitations insure continued dispute over the extent to which observed relationships between air pollution and respiratory damage are causal, as well as continued disagreement over the interpretation of negative studies. To resolve such disputes we must look for patterns and consistency across many studies, carefully performed and replicated under different circumstances. Decisions about the quality of the air we wish to breathe and the costs and risks we are willing to assume must ultimately be societal judgments, based on information from a broad range of good epidemiological and laboratory studies, and on consideration of competing demands for our resources.

SUMMARY

The existence of respiratory damage due to air pollution has been established beyond reasonable doubt by a large body of work. Nevertheless, little of the work that has been reviewed in this paper can be used to obtain reliable estimates of effects at specified levels. None of the data discussed in Tables 2 through 5 indicate that current or even moderately less stringent standards are inadequate to protect the public health. On the other hand, there is a dearth of reliable data indicating that standards can be relaxed.

Respiratory morbidity studies are more sensitive and reliable than are the corresponding mortality studies. Investigations comparing acute respiratory events with temporal pollutant fluctuations should continue, using better design, better analysis, and better exposure assessment techniques. The prognosis is poor for reliable quantitative data relating chronic pollutant exposure to respiratory damage. At present, cohort studies of changes in respiratory status vs careful measures of cumulative exposure, despite their cost, offer the best hope of obtaining these data. Such studies should be restricted to children and to adults who have never smoked.

ACKNOWLEDGMENTS

The author wishes to thank Yih-shih Yuh and Patricia Ford for advice and assistance in preparing this review. This work was supported by grants to the SIAM Institute for Mathematics and Society from the National Science Foundation, the Department of Energy, the Environmental Protection Agency, and the Rockefeller Foundation, by a Research Career Development Award from the National Institute of Environmental Health Sciences, and by grant number CA 23214-01 from the National Cancer Institute.

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